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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/894,788	08/27/1997	PAOLO GIACOMONI	05725.0213	9346

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EXAMINER

CHANNAVAJJALA, LAKSHMI SARADA

ART UNIT

PAPER NUMBER

1615

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/894,788

Applicant(s)

GIACOMONI, PAOLO

Examiner

Lakshmi S Channavajjala

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 8-21-01.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31-38, 40-54 and 56-66 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 31-38, 40-54 and 56-66 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Upon reconsideration, the finality of the rejection of the last Office action is withdrawn and the following rejection is presented.

Claim Rejections - 35 U.S.C. § 103

Claims 31-38, 40-54 and 56-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over 1) Hahn et al in view of Williamson et al; or 2) Hahn et al in view of Wahl et al; or 3) Hahn et al in view of Williamson et al and Wahl et al.

Hahn teaches a number of substances, which when applied topically can cause skin irritation. The substances include vehicles in which active ingredients are formulated (carriers), solvents, detergents, fragrances, propellants, salicylic acid derivatives, retinoids etc., and cause irritation which ranges from mild irritation to severe dermatitis conditions. Further, Hahn teaches that people with sensitive skin has an inherent predisposition to skin irritants, for example, people with skin conditions such as psoriasis, contact dermatitis etc., (see col. 3, lines 27-43). Hahn teaches strontium cation as an anti-irritant (see entire document, particularly, cols. 1-4, 10 and 11), suggesting in general the use of anti-irritant together with an irritant, in the same composition. However, Hahn fails to teach the claimed nitric oxide (NO) synthase inhibitor as anti-irritant.

Williamson teaches NO synthase inhibitors, such as methyl-, dimethyl or amino substituted guanidines, for the treatment of chronic and acute inflammatory conditions (column 2, lines 44-54; col. 3, lines 13-18). Williamson also recognizes N-monomethyl-L-arginine, as a NO synthase inhibitor (col. 1, lines 60-65). The acute and chronic inflammatory conditions taught by Williamson include dermatitis, drug reactions, sunburn, insect bites, burns (thermal,

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chemical and electrical) (column 3, lines 38-45). Williamson et al also teaches pharmaceutically acceptable diluents and carriers (see col. 11, lines 35-39), which according to Hahn et al are capable of producing skin irritation.

A skilled artisan would be motivated to incorporate NO synthase inhibitors as anti-irritants, in the place of strontium cation in the teachings of Hahn et al, and still be able to counteract the irritation because Williamson et al teach NO synthase inhibitors of are capable of inhibiting chronic and acute dermatitis, a skin condition caused by chemicals (which according to Hahn et al is caused due to irritation by various chemical substances). Thus, the teachings of both Hahn and Williamson et al have conditions such as skin irritations and dermatitis resulting from exposure to chemicals. Therefore, it would have been obvious for a skilled artisan to substitute the strontium cation of Hahn et al with NO synthase inhibitors of Williamson et al, with an expectation to inhibit the irritation by caused by the substances of Hahn et al.

Williamson does not teach topical application of nitric oxide synthase inhibitor. However, applying nitric oxide synthase inhibitors of Williamson et al as a topical formulation would have been obvious from the teachings of Hahn et al, or alternatively, it is within the scope of a skilled artisan at the time of the instant invention to use topical formulations of nitric oxide synthase inhibitors as first line of choice, with an expectation to produce a local effect because the conditions described i.e., dermatitis and skin inflammation is topical.

Wahl et al teaches treatment of chronic inflammatory conditions such as psoriasis (paragraph bridging cols. 3 and 4), by administering the specific nitric oxide synthase inhibitors

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of the instant claims (see col. 3, lines 39-68). Wahl teaches several routes of administration, including topical application (col. 6, lines 53-65). Thus, Wahl et al teaches the same skin conditions, which have a predisposition to be irritated upon exposure to common cosmetic and pharmaceutical products of Hahn et al, and suggests topical application of nitric oxide synthase inhibitors. Therefore, it would have been obvious for a skilled artisan at the time of the instant invention to use the nitric oxide synthase inhibitors of Wahl (and Williamson et al) in the topical composition of Hahn et al, with an expectation to inhibit the skin irritation caused by the various chemicals (Hahn et al).

Response to Argument

Applicants argue that Hahn is not generic with respect to the teaching of anti-irritants, as Hahn does not teach substitution of strontium cation with any other anti-irritant. Applicants also argue that examiner has not pointed to any teaching of Hahn that would have motivated a skilled artisan to replace the strontium cation of Hahn with a NO synthase inhibitor of Williamson or Wahl. Furthermore, applicants argue that Hahn discloses one method of treatment using one compound for one condition, while both Williamson and Wahl discloses a different method of treatment using different compound for a different condition.

The above arguments have been considered but they are not persuasive because, the combination of strontium cation and irritants (of Hahn et al) can be taken as a general theory for having an irritant and anti-irritant in the same composition. More specifically, Hahn states that it is highly desirable to identify compounds with anti-irritant activity, that reduces irritation caused

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by exposure to irritating chemicals, environmental conditions such as sun, wind etc., or due to intrinsic irritation associated with skin conditions such as psoriasis (col. 4, lines 56-63). The motivation to replace the strontium of Hahn et al with the nitric oxide synthase inhibitors of Williamson et al comes from the fact that both the references teach the treatment of same skin conditions (dermatitis, chemical and environmental irritation etc.). Williamson et al teaches nitric oxide synthase inhibitors as a treatment for dermatitis, sunburn etc., while Hahn teaches strontium chloride. Further, Hahn teaches that the nature of irritation could range from itching, burning, to edema and erythema, which is also seen in inflammation. Thus, the anti-irritant treatment of Hahn et al also applies to the inflammatory conditions (resulting from irritation), the conditions also taught by Williamson et al and Wahl et al. Therefore, it would have been obvious for a skilled artisan that NO synthase inhibitors (Williamson) are also effective anti-irritants for the treatment of dermatitis (Hahn and Williamson), caused due to chemical irritants.

Applicants also present an analogy of using an antibiotic or a decongestant for the treatment of sinus infection. Based on the analogy, they argue that the treatment of symptoms of disease is not the same as the treatment of the disease itself and therefore, the anti-irritants (treat symptoms) of Hahn cannot be replaced with the anti-inflammatory NO synthase inhibitors (treat disease condition) of Williamson et al or Wahl et al. However, the analogy does not apply to the instant combination of references because Hahn suggests that in addition to being anti-irritant, strontium may act to inhibit or modify the action of other irritation-inducing biological molecules such as eicosanoids or cytokines, that may otherwise may be activated by topical application of skin irritants (col. 5, lines 21-26). Thus, it is apparent from the teachings of Hahn

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that anti-irritant strontium is not merely treating irritation topically, but is also capable of inhibiting or modifying the cellular mechanisms caused by irritant-induced cytokines i.e., treat the cellular mechanisms that cause the disease condition. While Hahn et al does not specifically state inflammatory conditions, Williamson et al recognizes the fact that cytokines induce nitric oxide synthase resulting in the production of large amounts of nitric oxide, which in turn leads to acute and chronic inflammation (col. 1) and suggest NO synthase inhibitors inhibit inflammation caused in dermatitis conditions caused by exposure to chemicals.

Applicants argue that unlike Wahl and Williamson, Hahn fails to teach systemically decreasing or preventing nitric oxide formation, and Hahn only teaches counteracting superficial skin irritation caused by topically applied irritants. This argument is not persuasive because, all the references are directed to skin inflammatory conditions (dermatitis, psoriasis) caused by chemical or physical agents, and Williamson and Wahl suggest that the inflammation in dermatitis or psoriasis, respectively, involves the increased production of nitric oxide. Thus, a skilled artisan would expect an increased nitric oxide production in the dermatitis conditions taught by Hahn (caused by irritants) because Williamson et al teaches that inflammation is acute and chronic inflammation is seen in conditions such as dermatitis, insect bites, and also teach that the causes of the inflammation among others, include toxins and caustic substances. Accordingly, it would have been obvious for a skilled artisan to incorporate NO synthase inhibitors in the composition of Hahn, with an expectation to inhibit the nitric oxide production and thus provide an effective treatment for dermatitis, an inflammatory condition caused by exposure to chemicals. Further, Wahl suggests topical application of NO synthase inhibitors.

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Accordingly, a skilled artisan would have expected NO synthase inhibitors of Williamson and Wahl to be effective as cutaneous anti-irritants, in the composition of Hahn.

Applicants argue that without the present disclosure a skilled artisan would not have any reason to use strontium cation and NO synthase inhibitors interchangeably because, the chemistry of these anti-irritants is completely different. However, as explained above, both Hahn and Williamson teach the treatment of skin conditions such as dermatitis caused by skin irritants. Therefore, a skilled artisan would expect to provide an effective treatment for dermatitis either by administering strontium (of Hahn) or NO synthase inhibitors (of Williamson or Wahl).


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S Channavajjala whose telephone number is 703-308-2438. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-7924 for regular communications and 703-308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.



Lakshmi S Channavajjala
Examiner
Art Unit 1615 April 21, 2003



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